Remarks

Claims 1-45 were previously pending in the above-identified patent application.

In the current response, claims 1-22, 31-37, and 39-45 have been cancelled, the claims being directed to a non-elected invention.

Claims 23-25, 29, 30, and 38 have been amended to improve clarity, with all of the amendments being supported by the specification and claims as originally filed. No new matter has been introduced.

New claims 46-60 have been added, with all of these claims being dependent from independent method claim 29. The subject matter of new claim 46 is found in the specification at, for example, paragraph 0008 (page 2) and paragraph 0022 (page 6); new claims 47 and 48 at, for example, page 3, lines 3-18 and paragraph 32 (page 10); and new claim 50 at, for example, Tables 5-7 (pages 24-26). Support for new claims 51-60 is found in original claims 1-11.

Upon entry of the current amendment, claims 23-30, 38, and 46-60 will be pending in the application and under consideration by the office.

35 USC § 112, second paragraph - definiteness

In the Office action of January 12, 2009, claims 23-30 and 38 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. More specifically, the Office stated that claims 29-30 provide for use of KDPGal aldolases, but do not set forth any steps in the method, and it is unclear what the method intends to encompass. A related rejection was also made for claims 29 and 30 under 35 U.S.C. § 101, with the Office stating that the claimed recitation of a use, without setting forth any steps in the process, results in an improper definition of a process.

In response, Applicant has amended claims 29 and 30 so that a step in the method is positively recited.

The Office has also stated that claims 23-30 and 38 recite uncommon abbreviations.
In response, Applicant have amended claims 23-30 and 38 to include the full terms, followed by abbreviations.

In view of these amendments, Applicant respectfully submits that the rejections under 35 U.S.C. § 112, second paragraph, and 35 U.S.C. § 101, have been overcome, and respectfully requests withdrawal of the rejections.

35 USC § 112, first paragraph – written description

In the Office action of January 12, 2009, claims 23-30 and 38 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office pointed to various aspects of the application including (a) the method of using, reciting a genus of KDPGal aldolase, and (b) the disclosure of SEQ ID NOs:2, 4, and 6, in asserting that one of skill in the art would not recognize that the applicant was in possession of the invention recited in claims 23-30 and 38 under 35 U.S.C. 112, first paragraph.

The claimed methods involve the use of KDPGal aldolases for converting pyruvate and E4P to DAHP. The claims, of course, feature the use of a polypeptide, but the polypeptide that is claimed is not merely a claim to a collection of sequences encoding polypeptides, but requires that the polypeptides have KDPGal aldolase activity. Therefore, the claims inherently require that the polypeptides have sufficient structural and sequence features that allow them to function as KDPGal aldolases.

The Office stated:

> *KDPGal aldolase does not define any structural feature and amino acids commonly possessed by the genus. The specification does not define any structural features and amino acid sequences commonly possessed by each genus.*

However, such detailed structural features are not required in the instant claims. The claims do require that the compound has the general framework of a polypeptide, but functional language (i.e., KDPGal aldolase activity) is permitted and can be used to define the subject matter sought to be claimed. See MPEP 2173.05(g). The written description guidelines do not require that a claim reciting a polypeptide having a specific enzymatic activity also recite a specific polypeptide sequence.

In relation to this (see paragraph 0060, page 18), Applicant notes the prior art describes that KDPGal aldolase activities have been identified in many different microbial strains. Claim 23 recites that isolated KDPGal aldolases can be used in the claimed method, and such sources (e.g.,

the bacterial strains as described and known to those in the prior art) provide written description supporting the claim.

The application not only describes a large number of recombinant KDPGal aldolase sequences, but it also facilitates the identification of an even larger number of KDPGal aldolase sequences. The sequences as described, and the additional information teaching how to identify other KDPGal aldolase sequences fully support the written description requirement. As a basis for asserting lack of written description, the Office has implied the specification is limited to three KDPGal aldolase sequences:

> *The instant specification discloses KDPGal aldolases of the sequences SEQ ID No 2, 4, and 6).*

This assertion, however, is incorrect.

For example, as noted in paragraph 0071 (page 27) the application discloses twenty-one other KDPGal aldolase sequences that are based on the directed evolution of the *E. coli*, *K. pneumoniae*, and *S. tymphimurium* dgoA sequences. Also, as disclosed at page 29, lines 24-26, the DgoA family shuffling experiments produced another batch of seventy- two other KDPGal aldolase sequences that were analyzed.

The overall teaching of the application and the state of the art should also be taken into consideration when assessing written description. Given the sequence information provided by the prior art, the SEQ ID NO:2, 4, and 6 sequences, and the tools available to one of skill in the art at the time the invention was made, one of skill could identify other KDPGal aldolase sequences. For example, the specification at paragraph 0061 (pages 18-19) describes the identification of other KDPGal aldolase sequences from various microorganisms of existing genomic databases using SEQ ID NO:2, 4, and 6 as query sequences, and the basic local alignment search tools. Sequences identified from this search included those from *Caulobacter cresentus* CB15, *Agrobacterium tumefaciens*, *Ralstonia solanacearum*, *Bradyrhizobium japonicum*, *Brucella melitensis* and *Sinorhizobium meliloti*. Of course, one could perform additional basic local alignment searches using query sequences of one of SEQ ID NO:2, 4, and 6 to identify other KDPGal aldolases from electronic databases having genomic sequence information.

Alternatively, KDPGal aldolases could be cloned from genomic DNA preparations from target microorganisms using primers (e.g., degenerate) prepared from the sequence information

provided by SEQ ID NO:2, 4, and 6. These techniques are well established and one of skill in the art could readily identify other KDPGal aldolase sequences.

The information provided by the application show KDPGal aldolases having highly conserved and homologous structural motifs. This is contrary to the position the Office has taken:

> *KDPGal aldolase enzymes have widely differing structural, chemical, and physical characteristics. Each genus is highly variable because a significant number of structural differences exist.*

These statements are unsupported, conclusory, and disagreed with by the Applicant. The Office has not provided any factual information to back up these statements.

In support of the high sequence homology of the KDPGal aldolases, Applicant points to the following alignment of SEQ ID Nos 2, 4, and 6, made using the alignment tools described in the specification. Amino acid identity among all three sequences (at a certain position) is noted by an "*", and similarity (i.e., wherein a conservative substitution is found) is noted by a "+". The "↑" shows the locations of some of the more desirable mutations that enhance higher specific activity for (DAHP) formation, as recited in claim 1.

```
          1         2         3         4         5         6
          0         0         0         0         0         0
  ***** ************+********+******+**********+**  +* ***+++ ID/POS
2 MQWQTKLPLIAILRGITPDEALAHVGAVIDAGFDAVEIPLNSPQWEQSIPAIVDAYGDKA
  MQWQT LPLIAILRGITPDEALAHVGAVIDAGFDAVEIPLNSPQWE+SIP +VDAYG++A 88/95
4 MQWQTNLPLIAILRGITPDEALAHVGAVIDAGFDAVEIPLNSPQWEKSIPQVVDAYGEQA
  MQWQTNLPLIAILRGITPD+ALAHVGAV+DAGFDA+EIPLNSPQWEKSI  VV AYG +A 90/95
6 MQWQTNLPLIAILRGITPDDALAHVGAVVDAGFDAIEIPLNSPQWEKSISSVVKAYGGRA
          ↑                   ↑              ↑

                                          1         1         1
          7         8         9         0         1         2
          0         0         0         0         0         0
  ********+***** ** ***+*******+  ****+** ************+***+**+*
2 LIGAGTVLKPEQVDALARMGCQLIVTPNIHSEVIRRAVGYGMTVCPGCATATEAFTALEA
  LIGAGTVL+PEQVD LA MGC+LIVTPNI  EVIRRAVGYGMTVCPGCATA+EAF+AL+A 88/95
4 LIGAGTVLQPEQVDRLAAMGCRLIVTPNIQPEVIRRAVGYGMTVCPGCATASEAFSALDA
  LIGAGTVL+PEQVD+LA MGC+LIVTPNIQPEVIRRAV YGMTVCPGCATA+EAFSALDA 90/95
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```
6 LIGAGTVLKPEQVDQLAGMGCKLIVTPNIQPEVIRRAVSYGMTVCPGCATATEAFSALDA
                            ↑

          1         1         1         1         1         1
          3         4         5         6         7         8
          0         0         0         0         0         0
  *************** ** ******* ++ +*************** *** *********
2 GAQALKIFPSSAFGPQYIKALKAVLPSDIAVFAVGGVTPENLAQWIDAGCAGAGLGSDLY
  GAQALKIFPSSAFGP YIKALKAVLP ++ VFAVGGVTPENLAQWI+AGC GAGLGSDLY 88/95
4 GAQALKIFPSSAFGPDYIKALKAVLPPEVPVFAVGGVTPENLAQWINAGCVGAGLGSDLY
  GAQALKIFPSSAFGP YI ALKAVLPP+VP+FAVGGVTPENLAQWI AGCVGAGLGSDLY 90/95
6 GAQALKIFPSSAFGPGYISALKAVLPPDVPLFAVGGVTPENLAQWIKAGCVGAGLGSDLY
                                    ↑

          1         2
          9         0
          0         0
  ***************** ******+
2 RAGQSVERTAQQAAAFVKAYREAVQ
  RAGQSVERTAQQAAAFVKAYREAV+ 88/95
4 RAGQSVERTAQQAAAFVKAYREAVK
  RAGQSVERTAQQAAAFV AYREAVK 90/95
6 RAGQSVERTAQQAAAFVNAYREAVK
                  ↑
```

As can be seen, the KDPGal sequences show a remarkably high degree of homology (greater than 80% identity). These highly homologous sequences dictate that KDPGal aldolases have very similar structural characteristics. Further, the specification has already shown that these sequences have KDPGal aldolase activity. The specification also teaches that these sequences can be altered, with guidance from the application, to provide enhanced enzyme activity.

In view of this, Applicant asserts the written description requirement has been fulfilled. The Applicant is not required to provide an exhaustive listing of KDPGal aldolase sequences to meet the written description requirement.

MPEP 2163, which is referred to in the Office action, states:

> *The 'written description' requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." Capon v. Eshhar, 418 F.3d 1349, 1357, 76 USPQ2d 1078, 1084 (Fed. Cir. 2005).*

This case, *Capon v. Eshhar*, which is used by the MPEP to guide analysis under 35 USC 112 1st paragraph, dealt with the adequacy of written description of claims towards a chimeric gene

formed from an antibody variable domain protein sequence and a lymphocyte activation protein sequence. The Board (of Patent Appeals and Interferences of the USPTO) originally decided that the claim to the sequence lack patentability because the specification did not set forth the complete sequence of the chimeric gene. However this decision was remanded by the Federal Circuit court who determined that the Board misconstrued the precedent and failed to consider the state of knowledge and the science, which included knowledge of the sequences to be combined.

The court in *Capon* noted that the specification disclosed primer sequences that could be used to generate the gene sequences of interest, that such sequences can be isolated and joined by conventional methods (PCR or cloning by primer repair), and discussed various known procedures for identifying, obtaining, and linking DNA segments. The Board did not dispute that these methods could be carried out to provide the claimed sequences. In agreement with the precedent of Capon, KDPGal aldolases from a variety of other bacterial strains could be identified using conventional methods and known procedures given the extensive guidance provided by the specification and the showing of high degrees of homology.

The court in *Capon* agreed with the patent applicants in that, "the Board misconstrued precedent, and that precedent does not establish a *per se* rule requiring nucleotide-by-nucleotide re-analysis when the structure of the component DNA segments is already known, or readily determined by known procedures."

The court in *Capon* also noted that despite the PTO's argument of the claims being too broad because they may include inoperative species, applicant and patent owner point out that (i) ``they have provided an adequate description and exemplification of their invention as would be understood by persons in the field of the invention," (ii) ``biological properties typically vary," and (iii) ``their specifications provide for evaluation of the effectiveness of their chimeric combinations." The court also noted that, "It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention. *See* In re Angstadt, 537 F.2d 498 (CCPA 1976)."

In view of these remarks regarding the claimed subject matter, taken in view of the teaching of the current application, the MPEP guidelines for determining adequacy of written description, and current case law pertaining to this area of technology, Applicant respectfully requests that the

Office reconsider and withdraw the written description rejection under 35 U.S.C. 112, first paragraph.

35 USC § 112, first paragraph - enablement

In the Office action of January 12, 2009, claims 23-30 and 38 were also rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office stated that the method for converting pyruvate and E4P to DAHP, comprising contacting an isolated or recombinant KDPGal aldolase of sequence of SEQ ID NO: 4 with a solution containing pyruvate and E4P was enabled, but asserted that the method using any isolated or recombinant KDPGal aldolase was not enabled.

The Office stated that the claims encompass an extremely large number of enzymes. However, in response, the current claims reciting KDPGal aldolases are not merely directed to a particular polypeptide sequence and derivatives thereof without a requirement that the polypeptide sequence have a particular functionality. The term KDPGal aldolase carries significant weight, and KDPGal aldolase polypeptides have sufficient structural and sequence features that allow them to function KDPGal aldolases.

With regard to enablement, the Office has stated that the disclosure is limited to the polypeptide sequences of SEQ ID NO:2, 4, and 6. This assertion by the Office is also incorrect. Enzyme activity was demonstrated for twenty-one other KDPGal aldolase sequences that were identified from the directed evolution experiments of the *E. coli*, *K. pneumoniae*, and *S. tymphimurium* dgoA sequences (see paragraph 0071, page 27). Enzyme activity was also shown for KDPGal aldolase sequences identified in the DgoA family shuffling method. As disclosed in page 29, lines 24-26, the DgoA family shuffling produced another batch of seventy- two other KDPGal aldolase sequences that were analyzed.

While the Office has stated recombinant methods are known, it has also asserted that it is not routine in the art to screen for multiple substitutions or modifications as encompassed by the instant claims. However, as shown by the extensive experimental data as mentioned herein, the current application has indeed screened for multiple substitutions or modifications and identified a significant number of variants that have enzymatic activity. Using this information, the specification provides a guide to make additional variants having activity as well.

The Office has also asserted (on page 6):

> *...one skilled in the art would expect any tolerance to modification for a give protein to diminish with each further and additional modification, e.g. multiple substitutions.*

The experimental data of the application refutes this assertion. As shown in Tables 5-7, the Applicant has identified multiple amino acid positions, that when subject to substitution to alter the amino acid from the wild type sequence, actually increase enzymatic activity, as compared to the wild type levels.

Provided this guidance, and the demonstration of multiple KDPGal aldolase sequences (both wild type sequences and variants thereof), the specification enables one skilled in the pertinent art to make and use the claimed invention. Given the present disclosure, additional sequences providing KDPGal aldolase activity could be obtained. While such identification may be somewhat complex given molecular biology experimentation is involved, it is neither undue nor unreasonable. MPEP 2164.01.

Recent case law also supports enablement of the present claims. For example, Ajinomoto Co., Inc. v. Archer-Daniels-Midland Co. (228 F.3d 1338, 56 USPQ2d 1332; Fed. Cir. 2000), dealt with claims to a method for genetically modifying a bacterium to produce an amino acid. The method involved mutation of a bacterium to a donor strain, isolating the mutated gene from the bacterium, inserting the mutated gene into a recipient strain with mutations in both amino acid synthesis and metabolism genes. An accused infringer argued that the claims could cover a myriad of bacterial strains not yet known, however the court, in response, stated that the claims were enabled. "According to the record, all of the methods needed to practice the invention were well known to those skilled in the art. Despite the diversity existing among bacteria, practitioners of this art were prepared to carry out the identification, isolation, recombination, and transformation steps required to practice the full scope of the claims."

Like the present method, despite some diversity in the sequence of the KDPGal aldolases, the present specification shows significant regions of great identity between KDPGal aldolases, and a number of amino acid positions that can be altered to provide KDPGal aldolases with the comparable or enhanced enzyme activity. Given the information and

guidance provided by the specification, along with the tools available, one of skill could readily carry out the identification and isolation of other KDPGal aldolases, and use these in a method for the conversion of pyruvate and E4P to DAHP.

Another recent case pertaining to enablement, Falkner v. Inglis (448 F.3d 1357; Fed. Cir. 2006), dealt with a method for inactivating an ``essential" gene in a poxvirus vector. The patent set forth no working example or gene sequence. However, prior art publications described the poxvirus genome and the locations of ``essential regions." Testimony indicated that one skilled in the art would have been able to locate an ``essential" gene, even though that may have required extensive time and expense.

In yet another recent case pertaining to enablement, Monsanto Co. v. Scruggs (459 F.3d 1328; Fed. Cir. 2006), dealt with claims to insertion of synthetic gene, including a "CaMV" promoter, into plant DNA. The patents did not "cover one particular gene sequence," and the DNA sequences of several promoters were known in the art. An accused infringer asserted on appeal that the patent was invalid for not satisfying the enablement requirement. The accused infringer argued that the patent was not enabling because no particular gene sequence is claimed and because only one example of the entire genus of CaMV promoters is described in the specification.

In response, the patent holder replied that "more than one example of CaMV is described; the patent, for instance, refers to biological deposits of the CaMV strains that can be obtained to make the invention." And, "Moreover, because of the level of skill in the art and the publicly available information about CaMV, no specific gene sequence needed to be claimed for someone of ordinary skill in the art to understand how to make and use the invention."

The accused infringer argued that, at a minimum, one must disclose in the specification the exact DNA sequence of most species of the claimed genus. However, the court noted that the accused infringer, ``presented insufficient evidence to demonstrate that others would have been unable to practice the claimed invention without undue experimentation." "The fact that *some* experimentation may be necessary to produce the invention does not render the '605 patent invalid for lack of enablement. ... Because [the accused infringer] has failed to meet its burden of proof, it has not shown the ' 605 patent invalid for lack of enablement."

In view of these remarks regarding the claimed subject matter, taken in view of the teaching of the current application, the MPEP guidelines for determining adequacy of enablement, and current case law pertaining to this area of technology, Applicant respectfully requests that the Office reconsider and withdraw the enablement rejection under 35 U.S.C. 112, first paragraph.

Conclusion

Approval of the application and allowance of the claims are earnestly solicited. In the event that a phone conference between the Examiner and the undersigned would help resolve any issues in the application, the Examiner is invited to contact undersigned at 617-526-9841.

Respectfully Submitted,

Dated: July 10, 2009

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